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Solid Tumour Section

Short Communication

Kidney: ALK-rearranged renal cell carcinoma

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Abstract

Review on ALK-rearranged renal cell carcinoma, summarizing clinical and genetic data

Keywords
Renal cell carcinoma; ALK; HOOK1; TPM3; STRN; EML4; VCL

Identity

Phylum
Urinary system:Kidney: Renal cell tumors: :ALK-rearranged renal cell carcinoma

Classification

ALK-rearranged renal cell carcinoma is a distinct type of renal cell carcinoma included in the so-called emerging/provisional RCC. The 2013 International Society of Urological Pathology (ISUP) Vancouver Classification of (adult) renal neoplasia identified a category of emerging or provisional new entities. Although these entities appeared to be distinct, these are rare tumors not fully characterized and additional reports will be needed to refine their diagnostic criteria and established clinical outcome.

Clinics and pathology

Disease

ALK-rearranged renal cell carcinoma is a distinct emerging type of RCC that commonly affects children and young adults. The disease is defined as a RCC harboring ALK gene rearrangements, resulting in oncogenic fusions with a variety of partner genes.

Epidemiology

ALK-rearranged renal cell carcinoma is an uncommon type of RCC. Initially described in children, in which it may be over-represented, further investigations demonstrated that a small proportion of adult RCC belong to this ALK-rearranged category. Of 18 well-documented cases reported to date, 8 have been described in children (6-16 yo), and 10 in adults (33-61 yo). An association with sickle cell trait was observed in the first cases described, but this association seems inconsistent and may be limited to cases with a specific VCL/ALK gene fusion.

Clinics

These form masses in the kidney. The majority of cases described so far have been confined to the kidney with a median size of 4.5 cm. Nodal extension at presentation has been observed; distant metastases are rare and have been observed more commonly in adult patients. The clinical course of ALK-rearranged RCC is frequently indolent, although rare cases, more frequently in adult patients, pursue a more aggressive clinical course.

Pathology

Grossly, ALK-rearranged RCC are brown to tan solid masses that may be well circumscribed or

infiltrative, usually located centrally with extension into the renal pelvis. Histologically, the tumors most commonly feature a solid architecture, with occasional trabecular and tubular features, and are composed of sheets of epithelioid cells with abundant palely eosinophilic cytoplasm and frequent intracytoplasmic lumina. Cell nuclei show high-grade features, with vesicular chromatin and prominent nucleoli -usually ISUP grade 3, but occasionally ISUP grade 4. Rhabdoid morphology or intracytoplasmic inclusions may be focally present. There is a prominent capillary network. Less frequently, ALK-rearranged RCC may show a predominantly papillary architecture, mucin deposition and focal psammomatous calcification. It is unclear if some of this features correlate with specific fusion partners. Immunohistochemically, the tumor cells consistently express ALK, CK7, EMA, and TFE3 (which should not be interpreted as evidence of TFE3 rearrangement, absent in this tumor type); nuclear INI1 expression is retained.

Treatment

Treatment: surgical excision. Treatment with ALK inhibitors has provided clinical benefit in cases with advanced disease.

Cytogenetics

Cytogenetics Morphological

***ALK* Gene Fusions in renal cell carcinoma (RCC)**

Neoplasm	Fusion	Age Range (years) (n)
ALK-rearranged RCC	t(2;10)(p23;q22) ***VCL/ALK***	6-16 (3)
ALK-rearranged RCC	t(1;2)(q25;p23) ***TPM3/ALK***	12-49 (7)
ALK-rearranged RCC	inv(2)(p22p23) ***STRN/ALK***	33,38 (2)
ALK-rearranged RCC	inv(2)(p21p23) ***EML4/ALK***	52,53 (2)
ALK-rearranged RCC	t(1;2)(p32;p23) ***HOOK1/ALK***	16 (1)
ALK-rearranged RCC	***ALK/unknown***	44-61 (3)

Result of the chromosomal anomaly

Fusion Protein

Description

ALK-rearranged RCC are characterized by fusion of the ALK tyrosine kinase gene with one of several gene partners including VCL, TPM3, STRN, EML4, and HOOK1 (Table 1). The originally described translocation in ALK-rearranged RCC was t(2;10)(p23;q22) which fuses the 5' end of VCL to the 3' end of ALK. So far, VCL/ALK fusions have been described only in ALK-rearranged RCC - interestingly, in 3 tumors affecting pediatric patients with sickle cell trait. Similarly, HOOK1/ALK fusion has been identified only in RCC. The TPM3/ALK, STRN/ALK and EML4/ALK gene fusions, however, are similar to those found in other tumor types such as inflammatory myofibroblastic sarcoma, thyroid carcinoma and lung adenocarcinoma. All of these ALK gene fusions result in oncogenic proteins that include the kinase domain of ALK, fused to structural protein motifs that enable direct or indirect oligomerization. The ALK fusion partners also contribute active promoters that lead to strong expression of ALK, which can be detected by immunohistochemistry.

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